SCIENTIFIC ABSTRACT

Telomerase (hTERT) is an attractive candidate for a broadly expressed tumor rejection antigen since telomerase is silent in normal tissues but is reactivated and overexpressed in the majority of human solid tumors, including prostate cancers. We have shown that dendritic cells (DCs) transfected with mRNA encoding hTERT are effective stimulators of CTL and antitumor immunity. Data from an ongoing trial suggests that vaccination with hTERT RNA transfected DCs is capable of stimulating potent, hTERT-specific $CD8^+$ and $CD4^+$ T cell responses in virtually all patients. Vaccination was further associated with increased PSA doubling time and clearance of circulating tumor cells in some of the immunologic responders.

In this application, we propose to enhance the therapeutic impact of vaccination with hTERT RNA loaded DC by implementing a novel concept developed in our laboratory. We have shown that $CD4^+$ T helper cells carrying the IL-2 receptor α-chain (CD25), termed regulatory T cells, are capable of suppressing immune responses against tumors and self-antigens such as hTERT. Therefore, we propose a clinical trial in which we will administer the recombinant fusion protein denileukin difitox to deplete regulatory T cells in metastatic prostate cancer patients, followed by vaccination with LAMP hTERT RNA-transfected DC.

We hypothesize that *in vivo* depletion of $CD4^+$ $CD25^+$ regulatory T cell subsets will enhance the efficacy of hTERT RNA transfected DC to stimulate antigen-specific $CD4^+$ and $CD8^+$ T cell responses in patients with metastatic prostate cancer. Aside from the immunological analysis of the study subjects, we are interested whether this vaccination strategy will lead to an improvement of progression-free and overall survival. The results from this study will aid in the design of sufficiently powered phase II clinical trials aimed to determine the impact of hTERT RNA transfected DC vaccination to prolong progression-free and overall survival of subjects with metastatic prostate cancer.